

# **Assessing Generalizability of the Findings from EXCEL and NOBLE; Comparison with IRIS-MAIN Registry**

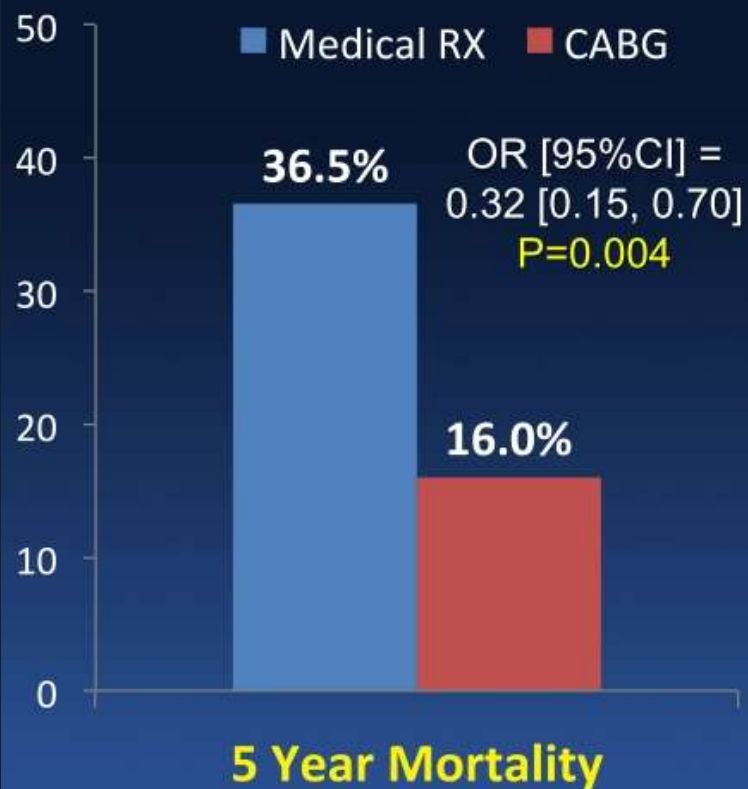
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# Data for Left Main

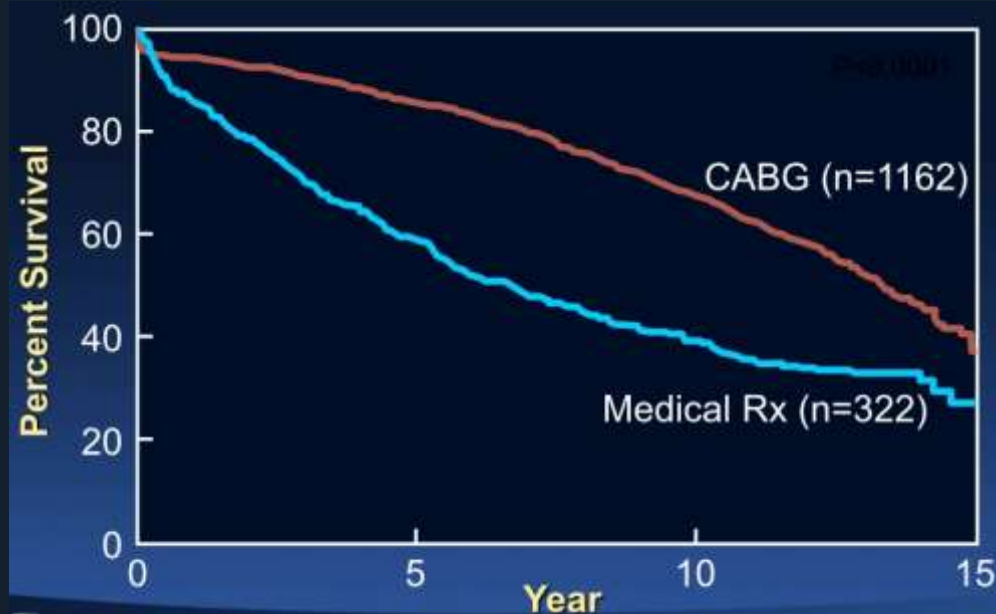
## 20 years ago

### CABG vs. Medical Rx (150 pts, VA and EU RCT)



Yusuf S et al. Lancet 1994; 344: 563-70

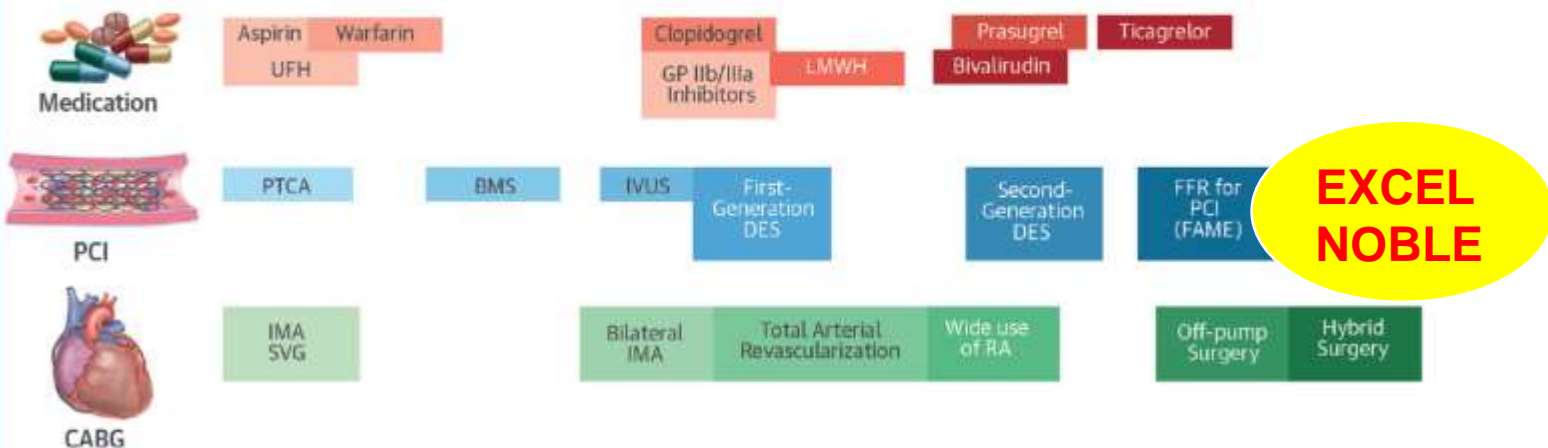
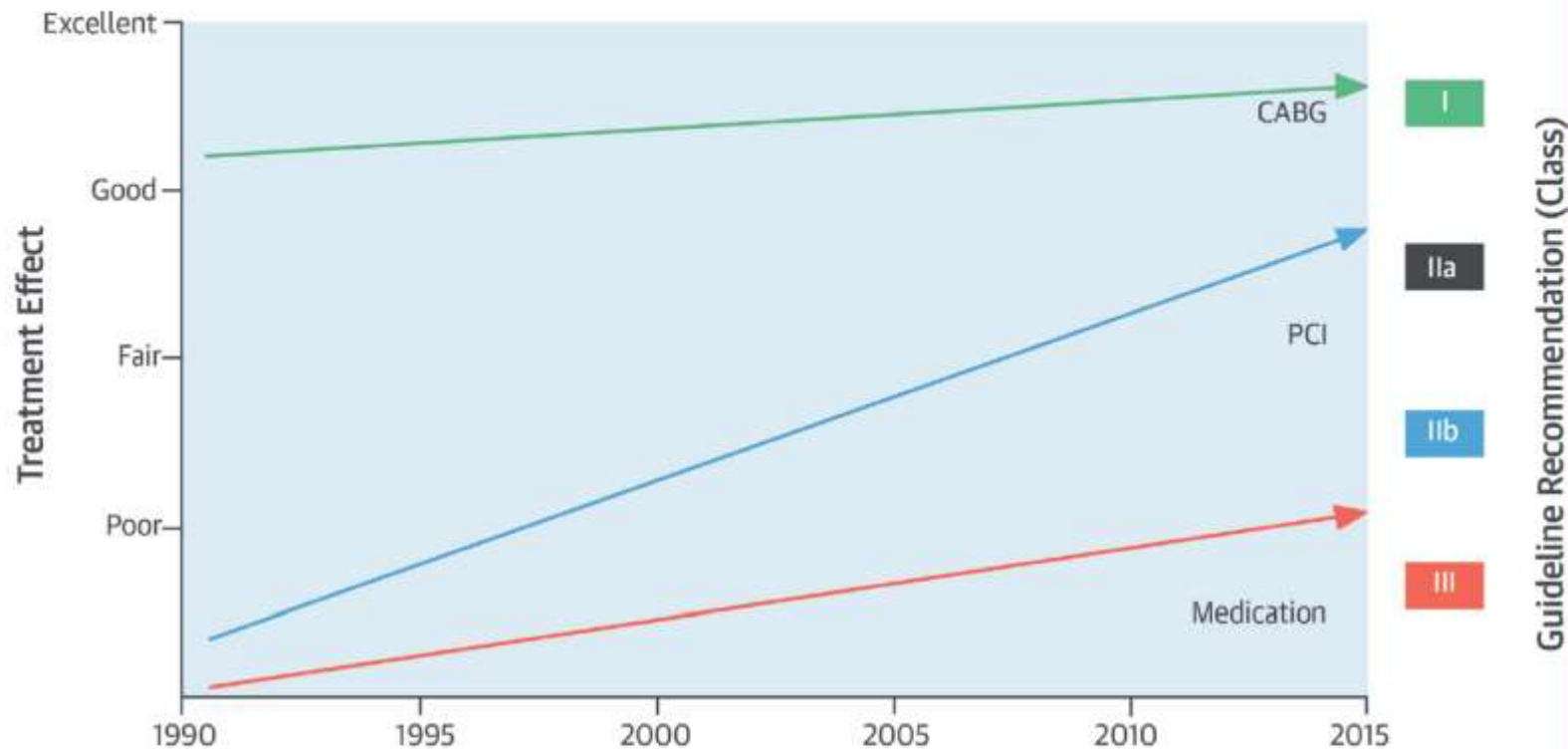
### CABG vs. Medical Rx (1484 pts, CASS Registry)



Yusuf S et al. Lancet 1994; 344: 563-70

**PTCA was not considered as an Tx option**

**CENTRAL ILLUSTRATION** Secular Changes of Treatment Effect and Guideline Recommendations in Relation to Medical Advances of Each Treatment Stratum for Left Main Coronary Artery Disease



Lee, P.H. et al. J Am Coll Cardiol. 2016;68(11):1233-46.

# Comparisons of PCI against CABG

*In 2<sup>nd</sup> DES era, finally released*

	Design	N (PCI/ CABG)	Sites	Recruitment period	Endpoint	FU, yrs	Stent type used for PCI
<b>NOBLE</b>	Multicenter RCT, non- inferiority	598/603	36 sites in northern Europe	Dec 2008 –Jan 2015	All-cause death, non- procedural MI, RR, or stroke	3.1 (2.0–5.0)	BioMatrix BES
<b>EXCEL</b>	Multicenter RCT, non- inferiority	948/957	126 sites in North/South America, Europe, AP	Sep 2010 –Mar 2014	All cause death, MI, or stroke	3.0 (2.4–3.0)	Xience EES

*Interesting similarities and differences*  
*Impact on practice **Beyond 2016?***

# Study Design

2900 pts with unprotected left main disease

SYNTAX score  $\leq 32$

Consensus agreement of eligibility and equipoise by heart team

Yes  
(N=1900)

No  
(N=1000)

Enrollment  
registry

Stratified by diabetes, SYNTAX score and center

R

PCI (Xience EES)  
(N=950)

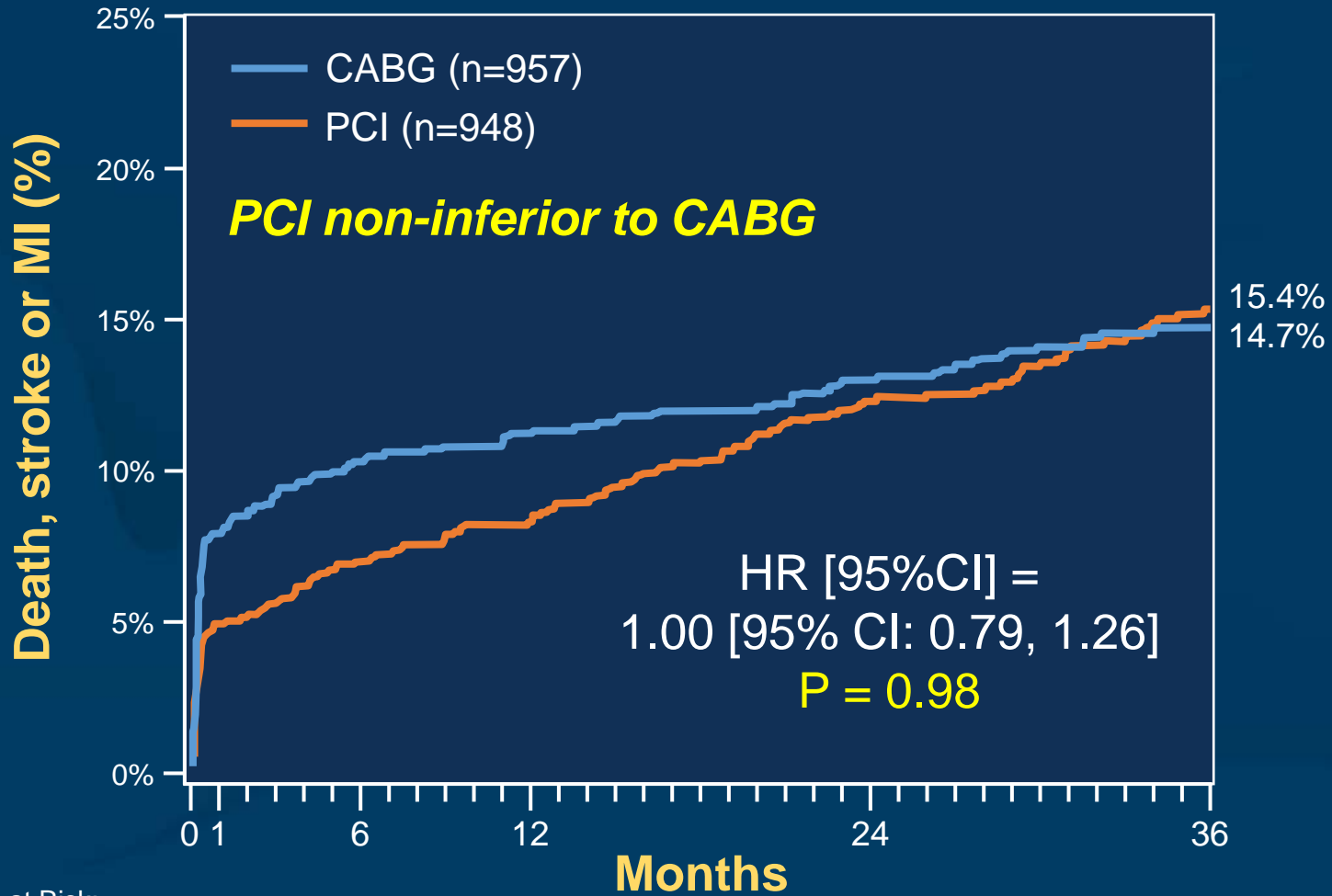
CABG  
(N=950)

Follow-up: 1 month, 6 months, 1 year, annually through 5 years

**Primary endpoint:** Measured at a median 3-yr FU, minimum 2-yr FU

# Primary Endpoint

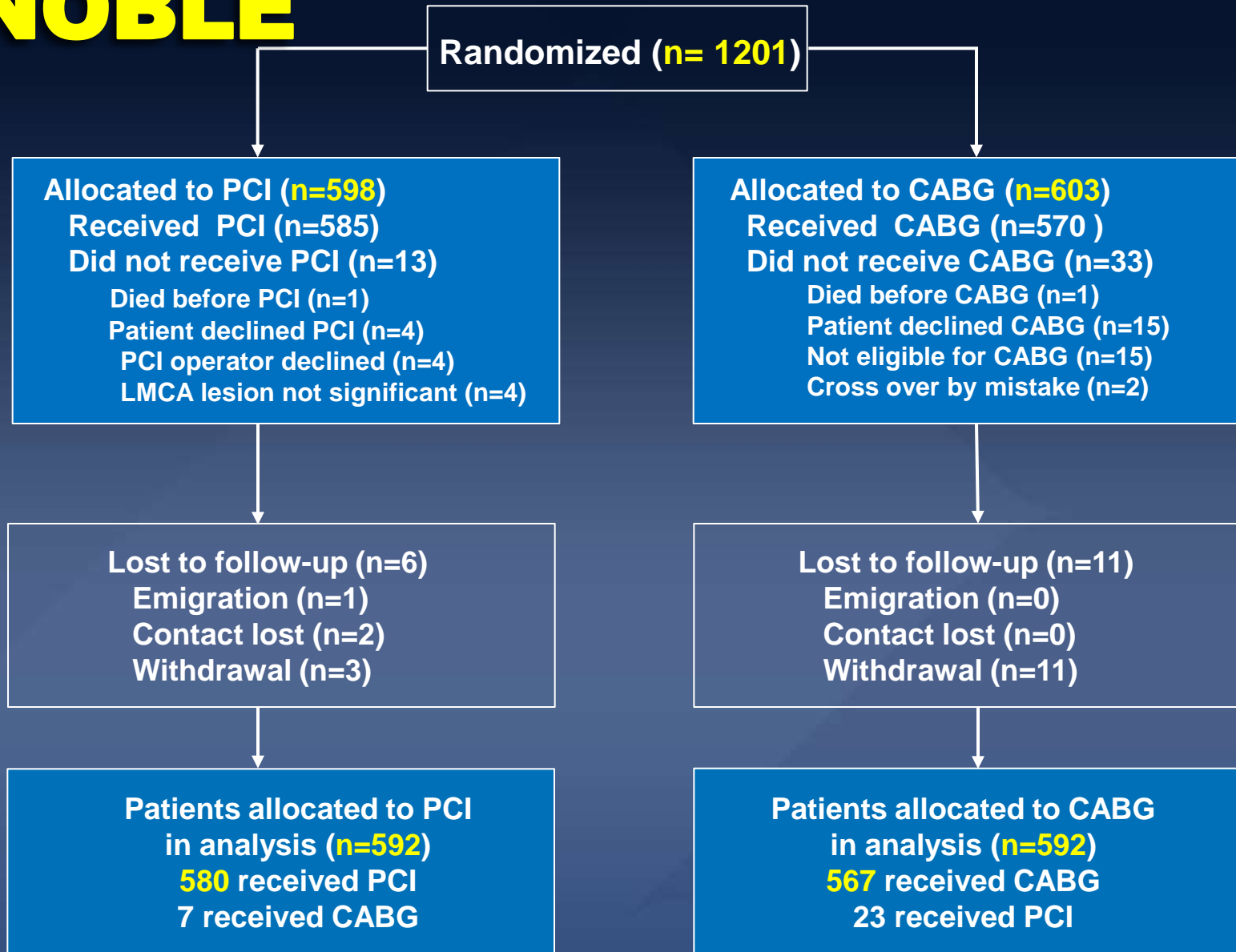
## Death, Stroke or MI at 3 Years



No. at Risk:

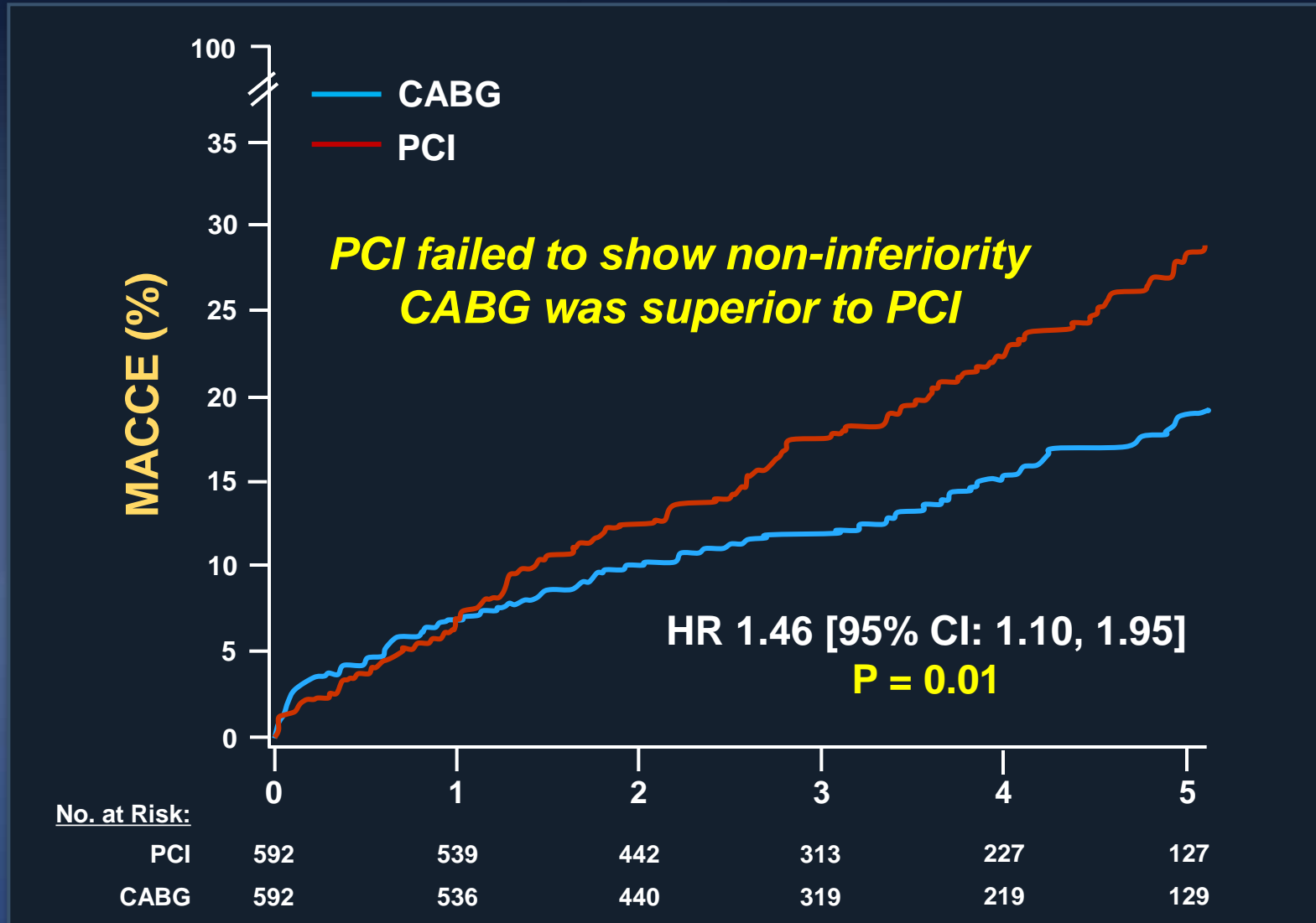
PCI	948	896	875	850	784	445
CABG	957	868	836	817	763	458

# NOBLE



# NOBLE

## Death, non-procedural MI, Stroke, or RR





# EXCEL vs. NOBLE Trial

Variables	EXCEL	NOBLE
Number of patients	1,905	1,201
Median follow-up	3 year	3.1 year
<b>HR(95%CI), CABG/PCI</b>		
Primary endpoint	1.0 (0.79-1.26)	<b>1.48 (1.11-1.96)</b>
All-cause death	1.34 (0.94-1.91)	1.07 (0.67-1.72)
Cardiac death	1.18 (0.74-1.87)	0.93 (0.45-1.92)
MI	0.93 (0.67-1.28)	<b>2.88 (1.40-5.90)</b>
Stroke	0.77 (0.43-1.37)	2.25 (0.93-5.48)
Revascularization	<b>1.72 (1.27-2.33)</b>	<b>1.50 (1.04-2.17)</b>

**NOBLE:** Stent thrombosis (3% NOBLE vs. 0.7% EXCEL), stroke (HR 2.25, p=0.07), non-procedural MI excluded (7% CABG vs. 5% PCI)

# Our Aim and Study Population

- To understand the similarities and differences, and assess the generalizability of EXCEL and NOBLE trial in real world setting.
- **The IRIS MAIN registry** is a nonrandomized, multi-national, multicenter observational study to assess the practice and outcomes of LM disease.
- All-comers design, consecutive patients with LM disease treated with medical Rx, PCI, or CABG



# Left Main Coronary Artery Disease

## Secular Trends in Patient Characteristics, Treatments, and Outcomes

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### ABSTRACT

Left main coronary artery (LMCA) disease is the highest-risk lesion subset of ischemic heart disease, and has traditionally been an indication for coronary artery bypass grafting (CABG). Recent evidence suggests comparable clinical outcomes between percutaneous coronary intervention (PCI) and CABG for LMCA disease, with similar rates of mortality and serious composite outcomes, a higher rate of stroke with CABG, and a higher rate of repeat revascularization with PCI. These results have been translated to the current guideline recommendation that PCI is a reasonable alternative to CABG in patients with low to intermediate anatomic complexity. However, how the characteristics, treatment, and clinical outcomes of patients with unprotected LMCA disease have evolved over time has not yet been fully evaluated. We therefore described secular trends in the characteristics and long-term outcomes of unprotected LMCA disease using “real-world” clinical experience from the IRIS-MAIN (Interventional Research Incorporation Society-Left MAIN Revascularization) registry together with a broad review of this topic. (J Am Coll Cardiol 2016;68:1233-46)

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# IRIS-MAIN Registry

- Between January 1995 and December 2013, a total of 5833 patients were enrolled from 50 academic and community hospitals in Asia (China, India, Indonesia, Japan, Malaysia, South Korea, Taiwan, and Thailand).

## *Three time periods*

- Wave 1 (BMS) for 1995–2002
- Wave 2 (First G DES) for 2003–2006
- Wave 3 (Second G DES) for 2007–2013

# Comparative Outcomes and Definitions

## *Outcomes for between –study comparison*

- Composite of death, MI, or stroke – 1 endpoint of EXCEL
- MACCE (death, MI, stroke, or RR) – 1 endpoint of NOBLE

## *Different definitions of MI between studies*

- **EXCEL:** Procedure related MI (any elevation of CK-MB >10 times URL, or >5 times plus evidence of ischemia), and sponMI (CK-MB or troponin >URL with evidence of ischemia)
- **NOBLE:** only non-procedural MI (increase in CK-MB or troponin >URL with ischemic symptoms or signs)
- **IRIS-MAIN:** Procedural related MI (CK-MB >5times URL plus evidence of ischemia), sponMI (CK-MB >URL with ischemic Sx or signs)

# Baseline Characteristics

	PCI Cohort				CABG Cohort			
	EXCEL (n=948)	NOBLE (n=592)	IRIS-MAIN (2 <sup>nd</sup> DES ) (n=1,707)	IRIS-MAIN (1 <sup>st</sup> DES ) (n=1,055)	EXCEL (n=957)	NOBLE (n=592)	IRIS-MAIN (2 <sup>nd</sup> DES ) (n=774)	IRIS-MAIN (1 <sup>st</sup> DES ) (n=964)
Age, yrs	66.0	66.2	64.4	62.4	65.9	66.2	65.2	63.7
Male sex, %	76.2	80.4	77.7	72.8	77.5	76.4	79.6	74.4
BMI, kg/m <sup>2</sup>	28.6	27.9	24.5	24.5	28.8	28.1	24.5	24.5
DM, %	30.2	<b>14.5</b>	33.7	33.4	28.0	<b>15.2</b>	42.2	38.4
HTN, %	74.5	65.2	63.8	55.7	73.9	65.7	66.7	54.8
Current smoker, %	24.1	18.2	23.8	25.1	20.8	21.4	26.6	27.2
HL, %	<b>71.5</b>	<b>81.5</b>	49.0	37.8	<b>69.3</b>	<b>78.4</b>	52.5	34.6
Previous MI, %	18.1	NA	6.6	8.8	16.9	NA	11.5	13.3
Previous stroke, %	5.5	NA	8.7	7.9	7.0	NA	9.2	7.0
Previous PCI, %	18.4	19.6	15.4	19.9	15.9	19.9	12.9	12.3
Previous HF, %	7.1	NA	2.6	2.4	6.2	NA	3.1	3.8
PVD, %	10.3	NA	4.5	2.8	8.8	NA	7.1	7.1
CLD, %	6.9	NA	2.4	2.7	8.5	NA	3.4	3.6
CKD*, %	17.6	NA	4.4	2.9	15.4	NA	4.9	3.5

# Baseline Characteristics

	PCI Cohort				CABG Cohort			
	EXCEL (n=948)	NOBLE (n=592)	IRIS-MAIN (2 <sup>nd</sup> DES ) (n=1,707)	IRIS-MAIN (1 <sup>st</sup> DES ) (n=1,055)	EXCEL (n=957)	NOBLE (n=592)	IRIS-MAIN (2 <sup>nd</sup> DES ) (n=774)	IRIS-MAIN (1 <sup>st</sup> DES ) (n=964)
Clinical indication, %								
Silent/Stable AP	60.8	82.1	40.8	44.2	60.5	82.9	43.5	25.9
ACS	39.2	<b>17.9</b>	59.2	55.8	39.5	<b>16.9</b>	56.5	74.1
Mean LVEF, %	57.0	60	59.0	60.2	57.3	60	55.3	56.4
Disease extent, %								
LM only	17.3	NA	10.8	13.8	17.8	NA	2.7	3.4
LM plus 1VD	31.0	NA	25.8	22.2	31.2	NA	5.8	8.4
LM plus 2VD	34.5	NA	36.3	31.2	31.5	NA	20.0	21.9
LM plus 3VD	17.2	NA	27.1	32.8	19.4	NA	71.4	66.3
LM location, %								
Ostium or shaft	18.2	19.4	33.0	43.1	20.8	18.6	27.5	36.5
Distal bifurcation	81.8	80.6	<b>67.0</b>	56.9	79.2	81.4	<b>72.5</b>	<b>63.5</b>
Right CAD, %	NA	NA	41.1	43.8	NA	NA	80.4	76.2
SYNTAX score	20.6	22.5	NA	NA		20.5	22.4	NA

# PCI characteristics

## PCI cohort

	EXCEL (n=935)	NOBLE (n=580)	IRIS MAIN (2 <sup>nd</sup> DES) (n=1,707)	IRIS MAIN (1 <sup>st</sup> DES) (n=1,055)
Stent technique, %				
Left main stenting only or simple crossover	NA	69.7	78.0	76.1
Two-stent technique	NA	31.4	22.0	23.9
Final kissing balloon	NA	54.5	29.7	38.5
Total stent number per patient	<b>2.4±1.5</b>	<b>2 (IQR; NA)</b>	<b>2.2±1.2</b>	<b>2.2±1.3</b>
Stent number in LMCA	NA	1 (IQR 1–2)	1.7±0.9	1.5±0.8
Total stent length per patient	<b>49.1±35.6</b>	<b>52 (IQR; NA)</b>	<b>52.3±34.1</b>	<b>45.5±33.0</b>
IVUS-guided PCI, %	<b>77.2</b>	<b>74.1</b>	<b>76.7</b>	<b>78.9</b>
Hemodynamic support, %	5.2	NA	5.0	3.5
DES type, %				
CoCr-EES	98.4	–	36.7	–
BES	–	89.1	8.4	–
PtCr-EES	–	–	22.1	–
Re-ZES	–	–	26.9	–
PC-ZES	–	–	1.9	–
Other 2 <sup>nd</sup> DES	–	–	4.0	–
SES	–	10.9	–	82.6
PES	–	–	–	17.4



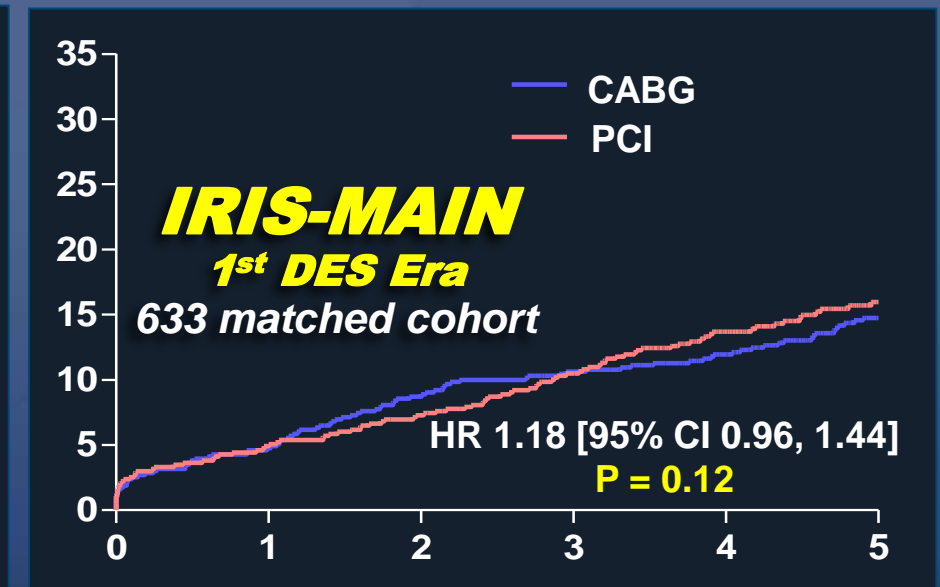
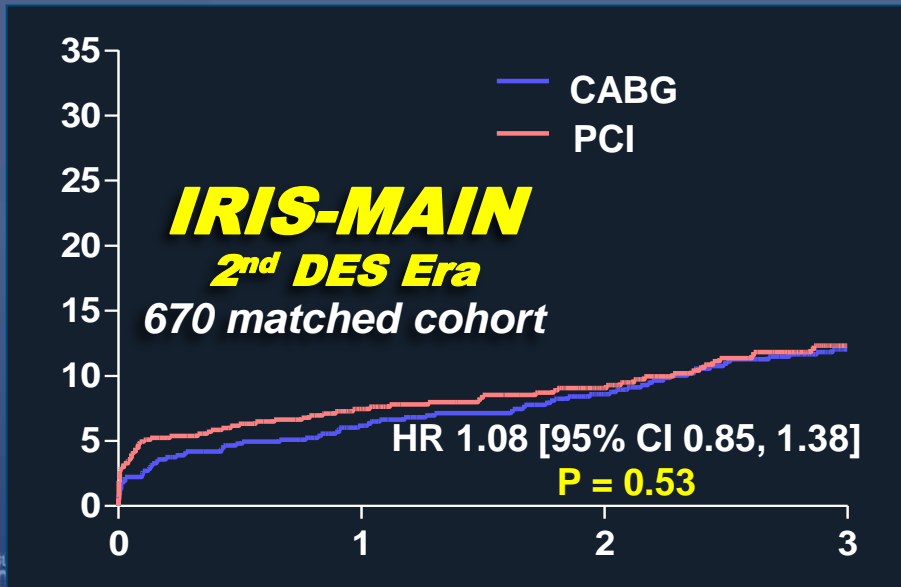
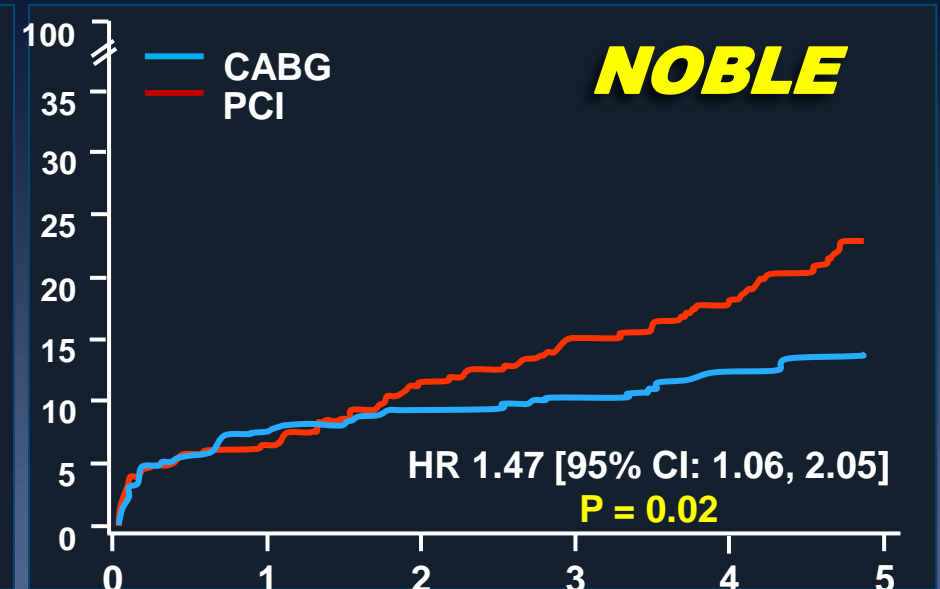
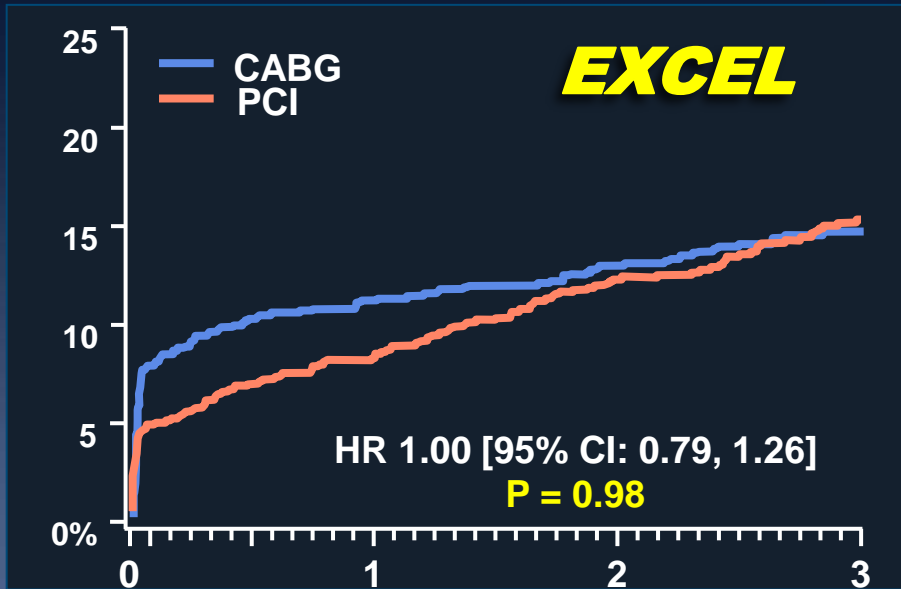
# CABG characteristics

## CABG cohort

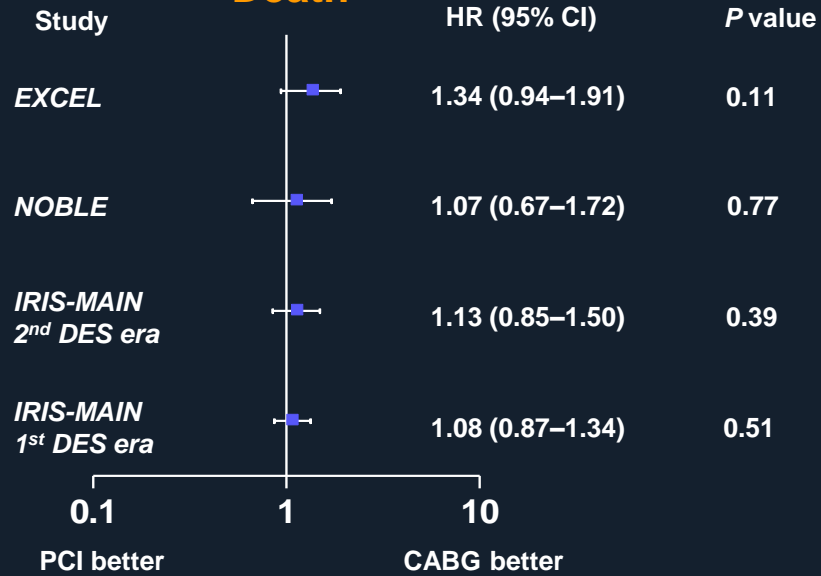
	EXCEL (n=923)	NOBLE (n=567)	IRIS MAIN (2 <sup>nd</sup> DES era) (n=774)	IRIS MAIN (1 <sup>st</sup> DES era) (n=964)
Off-pump surgery, %	<b>29.4</b>	<b>15.6</b>	<b>69.4</b>	<b>46.2</b>
No. of conduits per patient	2.6±0.8	2.5±0.7	2.9±0.9	2.9±1.0
No. of arterial grafts	1.4±0.6	NA	1.6±0.9	2.2±0.9
No. of vein grafts	1.2±0.9	NA	1.3±1.0	0.7±0.8
Use of internal mammary artery, %	98.8	93.1	94.2	95.3
Use of radial artery, %	<b>6.0</b>	<b>4.8</b>	<b>36.6</b>	<b>61.4</b>

# Death, MI, or Stroke

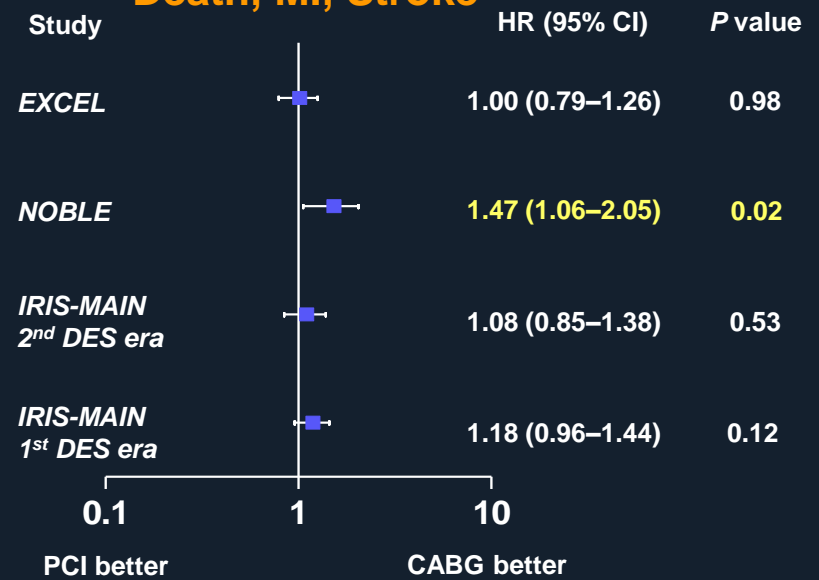
Compared with matched cohorts of IRIS-MAIN



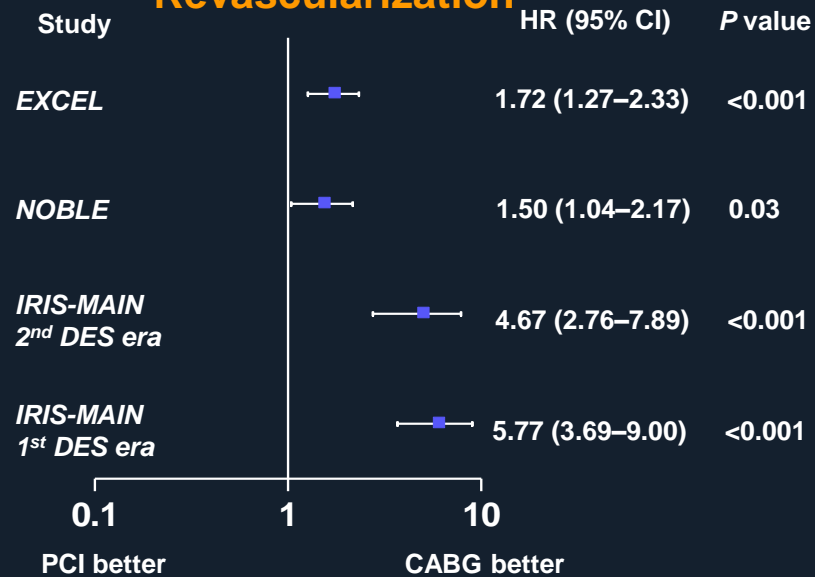
## Death



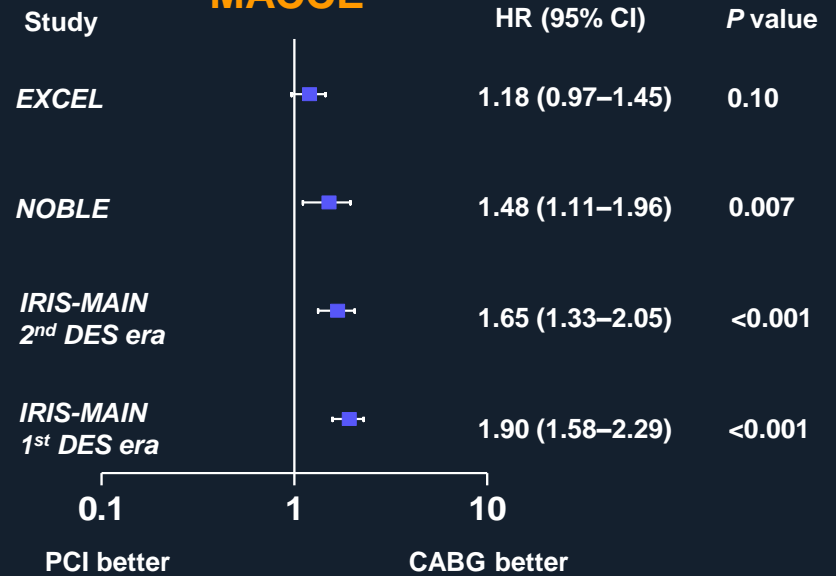
## Death, MI, Stroke



## Revascularization



## MACCE



# In Summary...

1. Baseline characteristics and results are relatively similar in EXCEL and in this large registry.
2. With respect to hard clinical endpoint (i.e., death, MI, or stroke), the results of the EXCEL trial and the IRIS-MAIN registry suggest that PCI with contemporary DES is an acceptable alternative to CABG who have clinical equipoise for either strategy of revascularization
3. EXCEL seems to be more generalizable than NOBLE in terms of patient inclusion and outcomes.

# Issues within Studies and limitations

## 1. NOBLE;

- 11% of PCI cohort received 1<sup>st</sup> generation DES.
- Excluded procedural MI; miss of important myocardial events
- Results extrapolated to a projected 5yr FU; preferentially represents the patient initially recruited
- High rates of stroke in PCI arm
- SYNTAX score did not work

## 2. EXCEL

- Does procedural MI really matter?
- Catch-up phenomenon of PCI curve at 3 years
- 24% of patients had a core lab defined high SYNTAX score

## 3. IRIS-MAIN is just one of the real world registry